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Values and preferences for oral antithrombotic therapy in patients with atrial fibrillation: physician and patient perspectives

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Abstract

Background Exploration of values and preferences in the context of anticoagulation therapy for atrial fibrillation (AF) remains limited. To better characterize the distribution of patient and physician values and preferences relevant to decisions regarding anticoagulation in patients with AF, we conducted interviews with patients at risk of developing AF and physicians who manage patients with AF.

Methods We interviewed 96 outpatients and 96 physicians in a multicenter study and elicited the maximal increased risk of bleeding (threshold risk) that respondents would tolerate with warfarin vs. aspirin to achieve a reduction in three strokes in 100 patients over a 2-year period. We used the probabilistic version of the threshold technique.

Results The median threshold risk for both patients and physicians was 10 additional bleeds (10 $P = 0.7$). In both groups, we observed large variability in the threshold number of bleeds, with wider variability in patients than clinicians [patient range: 0–100, physician range: 0–50]. We observed one cluster of patients and physicians who would tolerate <10 bleeds and another cluster of patients, but not physicians, who would accept more than 35.

Conclusions Our findings suggest wide variability in patient and physician values and preferences regarding the trade-off between strokes and bleeds. Results suggest that in individual decision making, physician and patient values and preferences will often be discordant; this mandates tailoring treatment to the individual patient's preferences.

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Introduction

Non-valvular chronic atrial fibrillation (AF) is the most common cardiac dysrhythmia[1,2] and is associated with substantial mortality and morbidity from stroke, thromboembolism and heart failure.[3] On average, two of every 100 patients untreated will have a stroke every year, and three will have severe disability or die prematurely.[1,4–6] Anticoagulants reduce the relative risk of strokes by more than a half.[7]

A systematic review found that 56–85% of patients with AF were not receiving anticoagulants.[8] As a result, every year thousands of patients suffer preventable strokes. The most common reason for not prescribing warfarin to patients with AF was, as in later studies,[9] clinicians' perception that patients were at high risk of bleeding.[8] This suggests that clinicians often believe the potential increased risk of bleeding outweighs the potential reduction in the risk of stroke. The impact of stroke on patients' lives raises questions about whether physicians' values reflect those of patients. The wisdom of withholding anticoagulation is further challenged by data suggesting that clinicians' ability to assess patients' risk of bleeding is poor.[10]

In considering warfarin prophylaxis, one needs to weight the benefits of stroke prevention against the burden and cost of taking warfarin, the burden of monitoring anticoagulation and the risk of bleeding. An alternative to warfarin, aspirin, is less effective, but it is also less likely to cause bleeding,[7,11] and requires no monitoring. One trial suggests dabigatran results in similar rates of stroke and systemic embolism as warfarin, as well as lower rates of major haemorrhage, without the inconvenience of monitoring.[12] A systematic review shows that in patients at high risk of stroke, anticoagulation is cost-effective, but not for those with a low risk of stroke.[13] The appropriate administration of thromboprophylaxis in patients with AF therefore needs to balance the risks and benefits and its cost-effectiveness.

The trade-off between stroke reduction on the one hand, and bleeding and burden of treatment on the other, makes the decision to use anticoagulant therapy preference dependent. Physician recommendations, driven by their own values and preference, may have considerable influence in patients' decisions regarding treatment and may lead patients to choose treatments contrary to their values and preferences.[14] These findings suggest the importance of ascertaining both physician and patient values and preferences.

Although there is substantial literature exploring patient values and preferences in the context of anticoagulation for AF,[15–19] exploration of physician values and preferences remains limited.[20] Limited prior results suggest patients are more stroke averse then clinicians, raising the possibility of underutilization of anticoagulation.[20] The findings of the study by Devereaux and colleagues, the main study documenting this discrepancy, may have at least partly resulted from methodological limitations, including failure to present the burden associated with warfarin use in sufficient detail and not including the risk of death through bleeding.[21]

To better characterize the distribution of patient and physician values and preferences pertinent to the decision making in starting anticoagulation prophylaxis in patients at risk of developing AF, we conducted interviews of patients and physicians' to elicit their preferences regarding anticoagulant stroke reduction in the face of the bleeding and burden associated with warfarin prophylaxis.

Methods

Setting and patients

A detailed description of our methods has been published elsewhere.[22] Briefly, from September 2008 to July 2009, we enrolled primary care outpatients from three geographically disparate regions in Spain, 60 years of age or older and at risk of developing AF (defined as presenting one or more of the following risk factors; hypertension, cardiovascular disease and diabetes).[6] We excluded patients with mini-mental

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state examination (MMSE)[23] score <24, history of AF and history of using warfarin (but not of antiplatelet agents). The Hospital de la Santa Creu i Sant Pau ethics board approved the study, and all patients provided informed consent.

Physicians

We randomly selected practicing clinicians working in general medicine (primary care, family medicine, internal medicine) and in cardiology. We excluded physicians if they were spending <30% of their time seeing patients or if they had not cared for a patient with AF in the preceding 6 months.

Health states

All interviews were conducted face-to-face. Participants read flip charts describing four health states: major and minor stroke, major bleeding and burden of treatment with aspirin or warfarin. We told participants that there was an equal likelihood of a major or minor stroke and described a non-fatal gastrointestinal bleeding event as the most common type of major bleed. We told participants that the risk of death with aspirin and warfarin was similar. Finally, we informed them that the risk of stroke presented included both ischaemic and haemorrhagic strokes. All this information is consistent with the best available evidence.[7,24]

Probability trade-off

Participants then completed a probabilistic version of the threshold technique (TT), which we refer to as the probability trade-off (PTO) exercise.[25] The process allows the identification of maximal increased risk of bleeding (i.e. the threshold) as a result of warfarin rather than aspirin use that respondents would be willing to tolerate to obtain the benefits in terms of stroke reduction in warfarin over aspirin. This exercise consisted of a series of scenarios presenting a fixed risk difference in strokes favouring warfarin over aspirin (five strokes with aspirin vs. eight strokes with warfarin in 100 patients over the period of 2 years) and a fixed risk of serious bleeding with aspirin (two gastrointestinal bleedings per 100 patients over 2 years).[11] The risk of bleeding associated with warfarin use was varied (Fig. 1).

In the first flipchart, we started randomly with either no additional bleeding with warfarin or with 17 additional bleeds over a period of 2 years. If participants decided that they would still take warfarin despite 17 additional bleeds, we increased the number of bleeds starting either at 18 additional bleeds or at 38. If they said they would still use warfarin at 38 bleeds, the exercise was terminated. If they declined warfarin at 38 bleeds, we asked for their choice at 18 bleeds. If they declined, we concluded their threshold was between 17 and

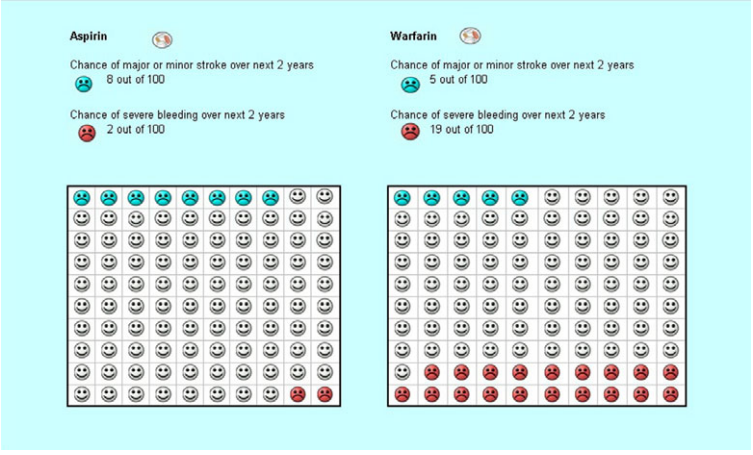

Figure 1 Probability trade-off exercise scenario.

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18 bleeds. If they continued to choose warfarin at 18 bleeds, we offered then the choice of warfarin or aspirin at 37 additional bleeds. If they chose warfarin, we concluded that their threshold was between 37 and 38 additional bleeds. We continued this alternating or ping-pong approach until we established their threshold for the number of bleeds – that is, the highest number of bleeds they would tolerate and still use warfarin.

If patients declined warfarin at 17 bleeds, we asked about their choice at 0 bleeds. If they declined warfarin, we concluded they were not willing to accept any bleeding risk. If they chose warfarin at 0 bleeds, we asked them to choose at 16 and then continued with the same ping-pong approach (1, 15, 2, 14, etc.) until we had established their threshold (i.e. the maximum number of bleeds they would accept and still use warfarin.

Feeling thermometer

Participants indicated the relative value they would place on a series of health states using a feeling thermometer (FT) and 100-mm. visual analogue scale with anchors: death (0) and full health (100). Participants used the FT to rate major and minor stroke, major bleeding and burden of treatment with aspirin and warfarin.

Presentation and roles

To account for order effects, with a computer-generated list, we randomized the order in which participants completed the exercises (PTO and FT), the number of initial bleedings (high or low) presented within the PTO exercise and the health states within the FT. We randomized clinicians to instructions that asked them to participate and complete the preference elicitation tasks as patients or as clinicians.[26]

Evaluation of the interview

At the end of the interview, with the use of a Likert scale, physicians were asked about their perceptions, the verisimilitude of the exercises and the potential usefulness of these exercises for clinical decision making.

Statistical analysis

Sample size

Our study was powered to determine differences in the treatment preferences of patients and clinicians. A sample size of 96 clinicians and 96 patients would provide more than 80% power to detect a difference between clinicians and patients $\geq$0.4 standard deviations (SD).

Key analyses

The distribution of the maximum number of bleeds that participants were willing to tolerate with warfarin, given a fixed stroke reduction (i.e. the threshold) was, in earlier studies, highly skewed.[20] Hence, we tested the difference of the medians in the threshold number of bleeding events acceptable between the patients and clinicians using a Mann–Whitney test.

We determined the extent of the association between patients' thresholds and their age, gender, location, education and knowledge of someone with a non-fatal gastrointestinal bleed or a stroke, and between physicians' thresholds and their age, gender, city of participation, specialty, years of practice, having taken care of a patient with AF using warfarin who had a non-fatal gastrointestinal bleeding or an intracranial bleeding and having taken care of a patient with AF not using warfarin who experienced a stroke. For this purpose, we used the Spearman correlation coefficient and Kruskal–Wallis test. We calculated means and 95% confidence intervals tested for feeling thermometer ratings of major and minor stroke, bleeding, burden, and cost in patients and physicians and tested for differences in mean values using a t-test and its corresponding 95% confidence interval (CI).

Results

Recruitment and characteristics of participants

We included 96 outpatients and 96 physicians (Tables 1 and 2). All of them completed the interview (Fig. 2). Table 1 presents patient demographic characteristics, including their

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Table 1 Demographic characteristics and education of participant patients

Characteristics of patients ($N = 96$)	
Age	71.7 (SD = 8.2) years
Women (%)	48 (50.0)
Education (%)	
None	23 (24.0)
Elementary	60 (62.5)
Secondary	8 (8.4)
Higher education	5 (5.2)
Knowledge of someone with a non-fatal gastrointestinal bleed (%)	21 (21.9)
Knowledge of someone with a stroke (%)	52 (54.2)

Table 2 Demographic characteristics and clinical experience of participant physicians

Characteristics of physicians ($N = 96$)	
Age	42.4 (SD = 16.7) years
Women (%)	41 (42.3)
Specialty (%)	
Family practitioner	43 (44.8)
Cardiologist	28 (29.2)
Internists	19 (21.9)
Other	3 (3.1)
Teaching activities (%)	41 (42.3)
Had a patient with AF on warfarin with a non-fatal gastrointestinal bleed (%)	52 (55.3)
Had a patient with AF on warfarin with an intracranial haemorrhage (%)	42 (46.7)
Had a patient with AF not on warfarin with a stroke (%)	62 (69.7)

education and knowledge of someone with a non-fatal gastrointestinal bleed or a stroke. Table 2 presents physicians' demographic characteristics and clinical experience, including previous experience with adverse events with patients on oral anticoagulation.

Probability trade-off

The median threshold (number of bleeds) acceptable, given a fixed 3% absolute reduction in stroke risk over 2 years, was similar between patients and physicians [10 (range: 0–100) and 10 (range: 0–50) $P = 0.7$]. The multimodal distribution showed that a greater proportion of patients than physicians had extreme values (Fisher's exact test, $P = 0.02$). Figure 3 shows the threshold for patients and physicians for the maximum risk of bleeding acceptable in 100 patients over a 2-year period with warfarin, given a fixed absolute reduction in the risk of stroke of 3%. Nineteen patients compared with six physicians were willing to accept more than 35 bleeds (33 or more extra episodes) in 100 patients over a 2-year period. Physicians responded similarly whether they saw themselves as patients or as clinicians (Table 3).

Physicians who looked after patients with AF using warfarin who had a non-fatal gastrointestinal bleed or with patients who suffered a stroke while not on warfarin were ready to tolerate a higher number of bleeds (10.1 vs. 16.3, $P = 0.002$ and 10.7 vs. 15.3, $P = 0.03$, respectively). No other factors were significantly associated with threshold.

Feeling thermometer

As in the bleeding threshold, there was wide variability (Fig. 4); the distribution of the values assigned to each health state was fairly similar for patients and physicians. Value on the 0 (death) to 100 (full health) was patient utilities were as follows: major stroke 21.5 (SD = 15.9); bleeding 44.0 (SD = 19.9); use of warfarin (65.9 [14.9]); use of aspirin (79.7 [19.1]). Physicians responded similarly whether answering as patients or physicians (Table 3). The greater the disutility of bleeding, the fewer the number of bleeds patients were willing to accept ($r = 0.24$; $P = 0.001$). This correlation was not observed in physicians. There was also an association between the burden associated with oral anticoagulants and the acceptable number of bleeds (the lower the value associated with anticoagulant, the lower number of bleeds acceptable).

Evaluation of the interview by physicians

Physicians felt comfortable with the different scenarios and the assumptions made (Table 4).

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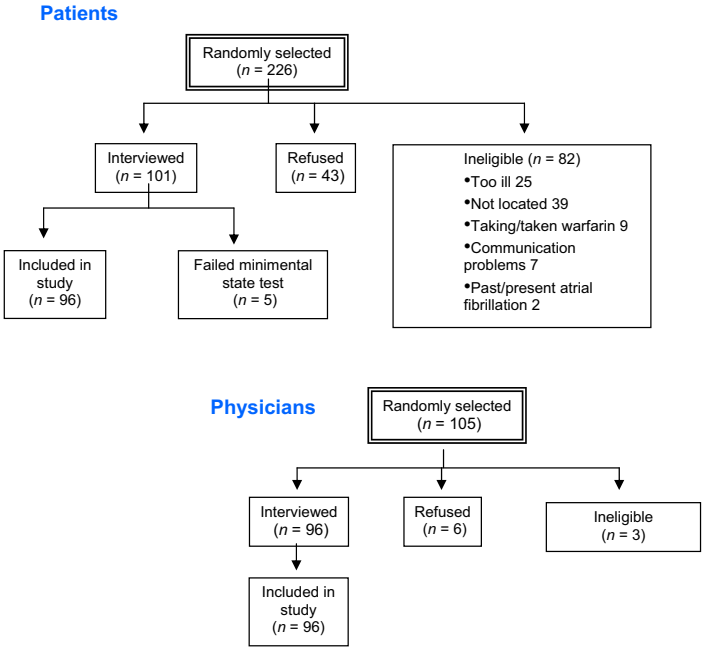

Figure 2 Study flowchart.

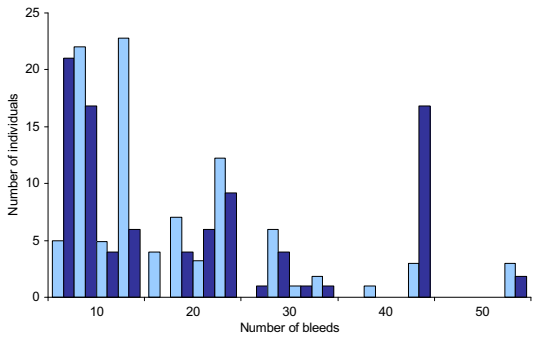

Figure 3 Number of gastrointestinal bleeds acceptable over a 2-year period for use of warfarin.

There was more discomfort with including both the risk of ischaemic and haemorrhagic stroke in the overall risk of stroke, and the perceived usefulness of the exercise to help patients with AF decide which treatment to take (Table 4).

Discussion

This study shows that patients, physicians answering in the role of patients and physicians participating as physicians have average similar levels of bleeding aversion, although more patients than physicians are highly stroke averse. Both patients and physicians show a multimodal distribution in their preferences (Fig. 3).

A cluster of patients and physicians would tolerate <10 bleeds, and another cluster of patients (but not physicians) would accept more than 35 bleeds (Fig. 3). Thus, there is an appreciable proportion of patients who are more stroke averse (and/or less bleeding averse) than virtually all physicians. It may be that we observed no corresponding group of physicians because physicians are more averse to outcomes for which they are responsible through acts of commission (bleeding) than adverse outcomes they failed to prevent by acts of omission (stroke).[27–30]

Given this wide variation in the bleeding threshold, we explored several a priori postulated factors that could explain differences among patients and physicians. Physicians who have taken care of patients with anticoagulants who experienced a non-fatal gastrointestinal bleed or patients with AF not on anticoagulants who experienced a stroke were ready to tolerate a higher number of bleeds. One expla-

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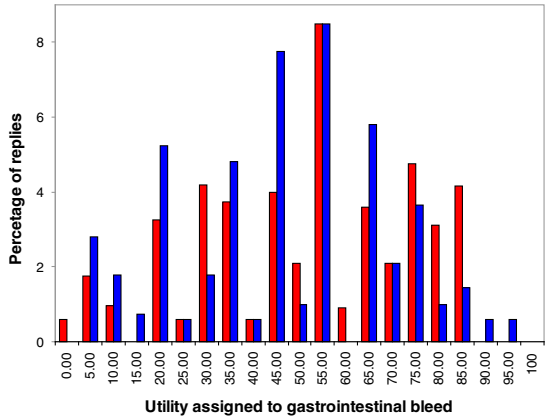

Figure 4 Value distribution for gastrointestinal bleeding (patients and physicians).

nation of the former result is that the fear of bleeding is actually greater in those who have not experienced a bleeding episode among their patients – although this is inconsistent with empirical findings suggesting that clinicians are more reluctant to prescribe warfarin after one of their patients' experiences a bleed.[30] Regret precipitated by a potentially reversible stroke could explain the second finding. Regardless of the true direction of the effect, physicians' should be aware that their values and preference may be very influential in decisions regarding anticoagulant therapy, pulling patients away from their preferred treatment options.[31] Therefore, they should help patients to identify the treatment option more consistent with their own preferences.

Strengths and limitations

Our study has several strengths. We designed a multicenter project and randomly selected patients and physicians from three geographically disparate regions in Spain. Our work took into consideration previous research and addressed some of the potential limitations of previous studies.[20] Our study has also some limitations. We did not include patients facing the real choice, for example patients having been recently diagnosed with AF. An alternative would have been to enrol patients with AF having already made a choice in the past. In patients with AF, however, cognitive dissonance (psychological discomfort due to inconsistent cognitions) might lead patients to modify their interpretation of the information provided to make it consistent with their previous decision.[32] We avoided the problem of patients previously exposed to information and making choices regarding antithrombotic treatment by including those at high risk of developing AF and excluding those with AF or a history of use of anticoagulants. A potential hypothesis is that this proximity to the possible necessity of a choice may have increased the likelihood that their responses reflected their true preferences.

Previous research

Our study aims to overcome potential limitations observed in previous research, and search for potential explanation of the observed differences between patients and physicians. In particular, Devereaux *et al.* found a large difference between physicians and patients (bleeding threshold for a fixed stroke reduction of 8% for 2 years of warfarin vs. no treatment: mean (SD) of 10.3 (6.1) for physicians and 17.4 (7.1) for patients).[20] We hypothesize that a number of limitations in the previous

Table 3 Health states ratings with the feeling thermometer

	Patients ($N = 96$) Mean (SD)	Physicians as patients ($N = 96$) Mean (SD)	Physicians ($N = 96$) Mean (SD)	P value
Major stroke	21.5 (15.9)	22.7 (18.7)	21.5 (16.9)	0.90
Minor stroke	47.2 (18.1)	45.3 (19.0)	47.2 (19.2)	0.82
Non-fatal gastrointestinal bleed	44.0 (19.9)	45.4 (19.7)	49.3 (21.6)	0.33
Taking warfarin daily	65.9 (14.9)	67.0 (16.6)	67.3 (21.0)	0.30
Taking aspirin daily	79.7 (19.1)	75.9 (23.1)	82.1 (18.4)	0.88

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Table 4 Evaluation of the interview by physicians

Questions	Rating (Likert scale: 1–5) Median (interquartile range)
To what extent did you feel comfortable with the different scenarios?	5 (1)*
To what extent did you feel comfortable with the use of happy and sad faces for the different outcomes?	3 (1)*
To what extent did the exercise reflected a real life situation?	3 (1)†
To what extent did you think it was real to assume that the risk of death is similar for aspirin and warfarin?	4 (1)†
To what extent did you feel comfortable with the fact that in the risk of stroke we included both the risk of ischaemic and haemorrhagic stroke?	3 (2)*
Usefulness of the exercise to help patients with atrial fibrillation decide which treatment to take	3 (2)‡
Seriousness of the fact that a patient of yours has a non-fatal gastrointestinal bleed due to a antithrombotic medication (aspirin or warfarin)	4 (1)§

*One being very uncomfortable to five being very comfortable.
†One definitely, five completely.
‡One no use, five very useful.
§One no importance, five very serious.

presentation of the scenario could be, in part, responsible for the differences between clinician and patient ratings. In particular, failure to present the inconvenience associated with anticoagulant use in sufficient detail could lead to an underestimation of its importance.[21] Our scenarios, unlike previous research, include comparison of warfarin and aspirin in the same scenario and a wider range of bleeding thresholds. Additionally, we implemented a multicenter design to minimize the influence of local views and used the FT to evaluate its correlation with the PTO. The more consistent results between physicians and patients, as well as the greater range of the bleeding thresholds, suggest that some of the discrepant findings are due to methodological limitations of the prior work.

The poor correlation between the PTO results and those of the ratings of disutility of stroke and bleeding raise questions about both physician and patient understanding of the choices they are making when completing these exercises. Other studies have also noted discrepancies between forced choice and utility or value-based methods.[33] It is possible that some of the wide difference in apparent preferences may be due to limited understanding in both groups, patients and clinicians.

Implications for practice and research

Our multicenter study was designed to overcome methodological limitations observed in previous research.[20,22] The results suggest wider variability in bleeding thresholds in the context of antithrombotic therapy for AF, both among patients and physicians than previously observed. Our results show similar levels of bleeding aversion, although more patients than physicians proved highly stroke averse. Qualitative research – as cognitive debriefing to help understand the 'why' of respondent preferences – could prove helpful in understanding the determinants of patient responses.[22,34] Our results confirm that patients are more stroke averse than are physicians, although the magnitude of the differences proved less than previously observed.

The large variability in both patient and physicians thresholds highlights the likelihood of a frequent mismatch between patient and physician values in the context of individual decision making. These results are likely to be directly applicable to the use of novel anticoagulants like dabigatran. Physicians are likely to often recommend against anticoagulation when patients would choose it, and patients are likely to be exposed to treatment they would not

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choose.[35] Further work exploring methods of enhancing understanding and informed choice, both for research and clinical practice, is required. Decision support technologies offer patients and clinicians a method to address this potentially serious problem.[36]

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Author contributions

PAC, VM, GG, PJD and HJS designed the study. GD, AID, GM, AIS, MR, JCS, SO, RR and BCV acquired data. PAC, VM, GG, PJD, HJS and IG analysed and interpreted the data. PAC, VM and GG drafted the manuscript. All authors revised the manuscript for important intellectual content and final approval of the version to be published.

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